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EXAMINER	
HUYNH, PHUONG N	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/615,437	Applicant(s) KIM, CHRISTOPHER M.	
	Examiner Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/15/02; 12/16/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 31-49* is/are pending in the application.

4a) Of the above claim(s) *1-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/15/02 has been entered.

2. Claims 1-10 and 31-49 are pending.

3. Claims 1-10 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 31-49 are being acted upon in this Office Action.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 31-37, 39 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Steigerwaldt *et al.* (1966, AS on PTO 1449).

Steigerwaldt *et al* teach a method of administering bee venom to a patient suffering from a condition such as Rheumatoid arthritis comprising administering to a patient simultaneously between 0.06 mg and 1.62 mg per injection of bee venom intradermally which is about 0.01 mg and about 1.0 mg per injection and one local anesthetic such as procaine hydrochloride in an amount of 0.2%, (that is 0.2 g/100 ml or 2 mg/ml) multiply by 0.1 cc or 0.1 ml per injection which is equivalent to 0.2 mg per injection which is about 0.3 mg per injection (See page 1047, column 1, Standardized Bee Venom, column 2 second paragraph, in particular). The Bee venom is dissolved or suspended in a liquid carrier such as an isotonic solution (See page 1047, 1047, column 1, Standardized Bee Venom, in particular). The reference solution is sufficient to provide 6 mg/ml (0.06 mg /0.1 ml *10), which is between 0.1 mg and 10.0 mg of bee venom per ml or about 5.0 mg per ml. The reference method of administered bee venom in an amount of 0.06 mg

and 0.54 mg which is about 0.05 mg and about 0.5 mg per injection (See page 1047, column 2, dosage schedule, in particular). The reference method teaches injecting bee venom in an amount of 0.18 mg, which is about 0.1 mg per injection (See page 1047, column 2, dosage schedule, in particular). The reference method also teaches administering an anesthetic such as procaine hydrochloride in an amount of 0.2% or 0.2 mg per injection, which is about 0.1 mg to about 0.3 mg per injection (See page 1047, column 1, in particular). Because the reference method uses a composition comprising the bee venom and the local anesthetic in the same range as the claimed composition, the reference composition inherently also reduces irritation, and inflammation of the patient which can be measure or visualize using an analog scale by at least 57 or to 28 or less. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 10/15/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) Steigerwaldt discloses the use of "procaine hydrochloride 0.2% as a local anesthetic". It cannot be interpreted as injecting 0.2% of procaine hydrochloride together with the standard bee venom simply because Steigerwaldt is silent on the mode of administration of procaine hydrochloride. In fact, the procaine hydrochloride can be administered by injection or by topical application or by both injection or topical application. Even assuming that Steigerwaldt teaches the injection of 0.2% procaine hydrochloride, it does not disclose the amount of procaine hydrochloride being used in each injection. The disclosure of injecting 0.1cc stand bee venom cannot be interpreted as injecting 0.1cc standard bee venom in a 0.2% procaine hydrochloride solution. The term "standard bee venom" as defined in Steigerwaldt does not include 0.2% procaine hydrochloride in it. An injection of "0.1cc stand bee venom" just means an injection of "0.1cc standard bee venom" and nothing else.

However, claim 31 still recites a method of ... administering to a patient simultaneously **or consecutively**. Assuming if Applicant's interpretation that the term "standard bee venom" as defined in Steigerwaldt does not include 0.2% procaine hydrochloride in it, the alternative of not administering the reference composition simultaneously would be administering the reference 0.2% procaine hydrochloride consecutively and thus the teachings of Steigerwaldt still anticipate the claimed invention.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 31-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steigerwaldt *et al.* (of record, 1966, AS on PTO 1449) in view of US Pat No 5,958,887 (Sept 1999, PTO 892), Kim *et al.* (Rhumatologic 41(3): 233-236, 1989; PTO 892), US Pat No. 5,226,901 (July 1993, PTO 892) and Koyama *et al* (Pain 84(2-3): 133-9, Feb 2000; PTO 892), Pat No 6,029,863 (of record, Feb 2000; PTO 892) and Cerrati *et al* (of record, A Therapeutic bee sting? Alternatives Complemetary Therapies page 57-58, Aug 1998; PTO 892).

The teachings of Steigerwaldt *et al* have been discussed supra.

The claimed invention in claim 31 differs from the teachings of the reference only that the method of reducing pain further comprising the steps of administering to a patient at least one anesthetic in an amount of about 0.1 mg to about 0.3 mg per injection wherein the administration of the bee venom and anesthetic reduces the pain of the patient by at least 57 on a visual analog scale.

The claimed invention in claims 37 and 38 differs from the teachings of the reference only that the method wherein the patient is suffering from a condition such as Multiple sclerosis.

The claimed invention as recited in claim 40 differs from the teachings of the reference only that the method wherein the local anesthetic is lidocaine.

The '887 patent teaches a method of reducing pain associated with DNA virus infection (See claim 1 of '887 patent, summary of invention, column 4, lines 32-34, in particular) by injection (column 3, line 66, in particular) or topically application (column 3, lines 64, in particular) of bee venom at a concentration of 120 μg/ml in 0.1 ml (or12 μg) which is about 0.01 mg per combined with a carrier such as human albumin in pharmaceutical injection to a patient (See column 4, lines 14-29, in particular). The '887 patent further teaches that the dosage of the active ingredient is within the purview one skilled in the art at the time the invention was made (See column 3, lines 46-48, in particular). The '887 patent further teaches that bee venom has been used in the management of arthritis, and multiple sclerosis (See column 1, lines 35-37, in particular).

Kim *et al* teach a method of reducing pain by administering bee venom to a patient suffering from a condition such as pain associated with rheumatoid arthritis or osteoarthritis wherein the bee venom is injected intradermally at 0.05 to 0.1 ml of standard BV-10 per injection to reduce pain of the patient by at least 57 on a visual analog scale where the degree of pain (VAS 50-60 is rated as moderate and 70-80 is rated as severe (See page 68, Methods, Fig 1, page 69, column 1, in particular). Kim et al teach that bee venom treatment significantly improves the relief of pain in 97 patients (See page 69, column 1, in particular) and increases in joint mobility (See page 71, Discussion, in particular).

The '901 patent teaches a method of reducing pain at the site of injection by administering buffered anesthetics such as lidocaine, mepivacaine, bupivacaine and NEUTRA-CAINE (See entire document, abstract, in particular) at a concentration lower than about 2.5 mcg/ml by intravenous injection or from about 0.25% to about 2.0% by weight of local injection (See column 18, claim 2 of '901 patent, columns 5-7in particular) or 0.5 to 1 wt % aqueous solution (See column 17, lines 15-19, in particular). The reference method further comprising a liquid carrier such as sodium bicarbonate in which the anesthetic dissolved or suspended (See column 2, lines 39-50, in particular). The '901 patent further teaches that the reference method is useful for reducing patient discomfort in patient in the form of "bee sting like" pain due to local pH related tissue irritation (See column 15, lines 13-15, in particular) and buffering anesthetic instantly before its use for reducing pain at the site of injection without sacrificing the normal two or more years of shelve life of these anesthetic (See column 2, lines 22-50, in particular).

Koyama *et al* teach that intradermal injection of bee venom such as melittin 5 microgram in saline resulted in pain at the site of injection where pain was measured using analogue scale (See abstract, in particular). The reference intradermal injection of melittin temporarily produces pain follows by sustained increase in skin temperature. Koyama *et al* further teach that topical application of anesthetics such as lidocaine is not effective for pain but markedly suppresses both the increase in the peak temperature and the area of temperature increase at the site of injection (See abstract, in particular).

The '863 patent teaches the use of local anesthetic such as 2 to 4% lidocaine as local anesthetic to reduce the pain and discomfort caused by the bee stings thereby "calming" the victim (See column 2, lines 6-10, column 2, line 55, in particular).

Cerrati *et al* teach the benefit of honeybee venom therapy includes rheumatoid arthritis, and multiple sclerosis. Cerrati et al teach melittin slows down the body's inflammatory response

inhibiting the amount of free radicals generated by tissues (See page 57, column 1, in particular). Cerrati *et al* teach the positive effects of bee venom on MS include less fatigue and fewer muscle spasms (See page 57, column 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer to a patient consecutively by injection intradermally of bee venom as taught by Steigerwaldt *et al,* Kim et al, Koyma et al or the '887 patent and substituting the anesthetic procaine hydrochloride as taught by Steigerwaldt *et al* for any anesthetic such as lidocaine as taught by the '901 patent, and '863 patent for a method of reducing pain in any patient suffering from a condition such as Rheumatoid arthritis or Multiple sclerosis as taught by Steigerwaldt et al, Kim et al, the'887 patent, and Cerrati *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Steigerwaldt *et al* teach bee venom is useful for a method wherein the patient suffering from a condition such as Rheumatoid arthritis. Kim et al teach that bee venom treatment significantly improves the relief of pain in osteoarthritis patient (See page 69, column 1, in particular) and an increase in joint mobility (See page 71, Discussion, in particular). The '901 patent teaches that any buffered anesthesia in sodium bicarbonate is useful for reducing pain associated with "bee sting like" injection due to local pH related tissue irritation (See column 15, lines 13-15, in particular). The '887 patent teaches that bee venom is useful for reducing pain associated with DNA virus infection (See claim 1 of '887 patent, summary of invention, column 4, lines 32-34, in particular). Cerrati *et al* teach the positive effects of bee venom on MS includes less fatigue and fewer muscle spasms (See page 57, column 2, in particular) and melittin slows down the body's inflammatory response inhibiting the amount of free radicals generated by tissues (See page 57, column 1, in particular).

One having ordinary skill in the art would have been motivated to not to administer anesthetics topically because Koyama *et al* teach that topical application of anesthetics such as lidocaine is not effective for pain but markedly suppresses both the increase in the peak temperature and the area of temperature increase at the site of injection (See abstract, in particular). The '863 patent teaches the use of local anesthetic such as 2 to 4% lidocaine as local anesthetic to reduce the pain and discomfort caused by the bee stings thereby "calming" the victim (See column 2, lines 6-10, column 2, line 55, in particular). The '901 patent teaches a

method of reducing pain at the site of injection of by administering buffered anesthetics such as lidocaine, mepivacaine, bupivacaine and NEUTRA-CAINE (See entire document, abstract, in particular). Koyama *et al* teach pain can be measure using visual analog scale. The term "57 on a visual analog scale" is relative and is not clear it is relative to what and tolerance of pain also varies from one patient to the next. The recitation of administering bee venom and anesthetic simultaneously is an obvious variation of administering bee venom and anesthetic consecutively as taught by Steigerwaldt *et al.*

Applicants' arguments filed 10/15/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) there is no suggestion or motivation to combine and not by the use of hindsight in view of the present application. (2) Even assuming that Steigerwaldt can be combine with Cerrati, the combination does not teach or suggest the use of such a small amount of anesthetic to "reduce the pain of the patient by at least 57 on a visual analog scale" (3) Steigerwaldt does not teach or suggest the use of an anesthetic in an amount of 0.1 to 0.3 mg per injection.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the use of bee venom to treat pain is taught by the '887 patent (See entire document). Steigerwaldt et al teach the use of bee venom and anesthetic to treat pain that is associated with inflammatory condition such as Rheumatoid arthritis. The use of bee venom to treat pain associated with Rheumatoid arthritis and Multiple sclerosis is taught by Cerrati *et al.* The '901 patent the use of buffer anesthetic for reducing patient discomfort in patient in the form of "bee sting like" pain due to local pH related tissue irritation (See column 15, lines 13-15, in particular) and buffering anesthetic instantly before its use for reducing pain at the site of injection without sacrificing the normal two or more years of shelve life of these anesthetic (See column 2, lines 22-50, in particular).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on

obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to Applicants' argument that the combination does not teach or suggest the use of such a small amount of anesthetic to "reduce the pain of the patient by at least 57 on a visual analog scale", The '901 patent teaches a method of reducing pain at the site of injection by administering buffered anesthetics such as lidocaine, mepivacaine, bupivacaine and NEUTRA-CAINE (See entire document, abstract, in particular). Koyama *et al* teach pain can be measure using visual analog scale. Kim *et al* teach a method of reducing pain by administering bee venom to a patient suffering from a condition such as pain associated with rheumatoid arthritis or osteoarthritis wherein the been venom is injected intradermally at 0.05 to 0.1 ml of standard BV-10 per injection to reduce pain of the patient by at least 57 on a visual analog scale where the degree of pain (VAS 50-60 is rated as moderate and 70-80 is rated as severe (See page 68, Methods, Fig 1, page 69, column 1, in particular). Further, the term "57 on a visual analog scale" is relative and is also within the range of VAS as taught by the Kim et al.

In response to Applicants' argument that Steigerwaldt does not teach or suggest the use of an anesthetic in an amount of 0.1 to 0.3 mg per injection, the '901 patent teaches that standard local anesthetics come in the form of 0.25% to 0.75% in solution (See column 5, in particular) and serum lidocaine levels exceeded 2.5μg/ml within 5 minutes following intravenous injection is toxic as lidocaine cross the placenta and intradermal or subcutaneous injection is not likely to induce toxic blood level (See column 15, lines 1-12, in particular). Koyama *et al* teach that topical application of anesthetics such as lidocaine is not effective for pain but markedly suppresses both the increase in the peak temperature and the area of temperature increase at the site of injection (See abstract, in particular). From the combined teachings of the '901 patent, Koyama *et al* and Steigerwaldt et al, the recitation of the use of anesthetic in an amount of 0.1 to 0.3 mg per injection is within the purview of one ordinary skilled in the pharmaceutical art at the time the invention was made as taught by the '901 patent, Koyama *et al* and Steigerwaldt *et al*.

9. Claims 42-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steigerwaldt *et al* (1966, AS on PTO 1449) in view of Banks *et al* (Chemistry and Pharmcology of Honey-bee venom In: Piek T, ed. Venoms of the Hyemoptera. London: Academic Press; 1986, pages 329-416. PTO 892), Kim *et al.* (Rhumatologic 41(3): 233-236, 1989; PTO 892), US Pat No. 5,226,901 (July 1993, PTO 892), Pat No 5,958,887 (Sept 1999, PTO 892), Koyama *et al* (Pain 84(2-3): 133-9, Feb 2000; PTO 892) and Cerrati *et al* (of record, A Therapeutic bee sting? Alternatives Complemetary Therapies page 57-58, Aug 1998; PTO 892).

The teachings of Steigerwaldt *et al* have been discussed supra.

The claimed invention as recited in claim 42 differs from the teachings of the reference only that the bee venom comprises about 40%-50% of melittin or about 1.5-2% of hyaluronidase in dry weight or wherein the venom exhibits about 40 to about 100 HHU/ml of Hayalouronidase activity when diluted to 100mcg/ml or is capable of inhibiting gelatin induced aggregation of erythrocytes of about 3-5mm/H wherein the administration of said anesthetic reduces the irritation associated with the injection of bee venom; wherein the administration of the bee venom and anesthetic reduces the pain of the patient by at least 57 on a visual analog scale.

The claimed invention as recited in claim 43 differs from the reference only by the recitation that the bee venom further comprises about 1.5-2.0% of hyaluronidase in dry weight.

The claimed invention as recited in claim 44 differs from the reference only by the recitation that the bee venom exhibits about 40 to 100HHU/ml of Hyaluronidase when dilute to about 100mcg/ml.

The claimed invention as recited in claim 45 differs from the reference only by the recitation that the bee venom is capable of inhibiting gelatin induced aggregation of erythrocytes of about 3-5mm/H.

The claimed invention as recited in claim 46 differs from the reference only by the recitation that the bee venom includes between about 80 to about 9,5000mcg total protein per ml.

The claimed invention as recited in claim 47 differs from the reference only by the recitation that the bee venom contains between about 0.01 to about 0.10mg of melittin and about 400 to about 4,500 mcg total proteins per ml.

The claimed invention as recited in claim 48 differs from the reference only by the recitation that the bee venom contains between about 0.04 to about 0.05mg of melittin and about 800 to about 950mcg total protein per ml.

The claimed invention as recited in claim 49 differs from the reference only by the recitation that the bee venom comprises about 40% - 50% of melittin.

Bank *et al* teach melittin is the major component of bee venom, which accounts for about 40%-50% in dry weight, and hyaluronidase accounts for about 1-2% in dry weight of the whole venom (See page 349, Melittin, page 344, Table II, page 337, in particular). Bank *et al* teach commercially available bee venom is that of the common European honeybee Apis melifera and some 98% of the dry weight of bee venom are known (See page 334, first paragraph, page 335, last paragraph, in particular). Bank et al teaches Melittin has anti-inflammatory mechanism and this may be why therapeutic properties have long been attributed to bee venom, especially in arthritic conditions (Seep age 403, first paragraph, in particular). Bank *et al* teach that starting with 50 mg, only 1 mg of hyaluronidase could be produced if the purification produced a 100% yield (See page 344, second paragraph, in particular).

Kim *et al* teach a method of reducing pain by administering bee venom to a patient suffering from a condition such as pain associated with rheumatoid arthritis or osteoarthritis wherein the been venom is injected intradermally at 0.05 to 0.1 ml of standard BV-10 per injection to reduce pain of the patient by at least 57 on a visual analog scale where the degree of pain (VAS 50-60 is rated as moderate and 70-80 is rated as severe (See page 68, Methods, Fig 1, page 69, column 1, in particular).

The '901 patent teaches a method of reducing pain at the site of injection of local parenteral anesthetic such as lidocaine, mepivacaine, bupivacaine and NEUTRA-CAINE (See entire document, abstract, in particular) at a concentration lower than about 2.5 mcg/ml by intravenous injection or from about 0.25% to about 2.0% by weight of local injection (See column 18, claim 2 of '901 patent, columns 5-7in particular) or 0.5 to 1 wt % aqueous solution (See column 17, lines 15-19, in particular). The reference method further comprising a liquid carrier such as sodium bicarbonate in which the anesthetic dissolved or suspended (See column 2, lines 39-50, in particular). The '901 patent further teaches that the reference method is useful for reducing patient discomfort in patient in the form of "bee sting like" pain due to local pH related tissue irritation (See column 15, lines 13-15, in particular) and buffering anesthetic instantly before its use for reducing pain at the site of injection without sacrificing the normal two or more years of shelve life of these anesthetic (See column 2, lines 22-50, in particular).

The '887 patent teaches a method of reducing pain associated with DNA virus infection (See claim 1 of '887 patent, summary of invention, column 4, lines 32-34, in particular) by

injection (column 3, line 66, in particular) or topically application (column 3, lines 64, in particular) of bee venom which contains 120 μg/ml in 0.1 ml (or12 μg) which is about 0.01 mg per combined with a carrier such as human albumin in pharmaceutical injection to a patient (See column 4, lines 14-29, in particular). The '887 patent further teaches dosage of the active ingredient is within the purview one skilled in the art at the time the invention was made (See column 3, lines 46-48, in particular). The '887 patent further teaches that bee venom has been used in the management of arthritis, and multiple sclerosis (See column 1, lines 35-37, in particular).

Koyama *et al* teach that intradermal injection of bee venom such as melittin 5 microgram in saline resulted in pain at the site of injection where pain was measured using analogue scale (See abstract, in particular). The reference intradermal injection of melittin temporarily produces pain follows by sustained increase in skin temperature. Koyama *et al* further teach that topical application of anesthetics such as lidocaine is not effective for pain but markedly suppresses both the increase in the peak temperature and the area of temperature increase at the site of injection (See abstract, in particular).

Cerrati *et al* teach the benefit of honeybee venom therapy includes rheumatoid arthritis, and multiple sclerosis. Cerrati et al teach melittin slows down the body's inflammatory response by inhibiting the amount of free radicals generated by tissues (See page 57, column 1, in particular). Cerrati *et al* teach the positive effects of bee venom on MS include less fatigue and fewer muscle spasms (See page 57, column 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the bee venom as taught by Steigerwaldt *et al* or Kim *et al* for the bee venom that comprises about 40%-50% of melittin or about 1.5-2% of hyaluronidase in dry weight as taught by Bank *et al* for a method of administering bee venom to a patient simultaneously or consecutively between 0.06 mg and 1.62 mg per injection of bee venom intradermally, which is about 0.01 mg and about 1.0 mg per injection and one local anesthetic wherein the bee venom comprises about 40-50% of melittin or about 1.5 to 2.0% of hyaluronidase as taught by Bank *et al* and any anesthetic as taught by Steigerwaldt *et al* or the '901 patent wherein the administration of said anesthetic reduces the irritation at the site of injection as taught by the'901 patent and reduce the pain of the patient that can be measure using a visual analog scale as taught by Koyama *et al* or Kim *et al*. From the combined teachings of the

references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Steigerwaldt *et al* teach bee venom is useful for a method wherein the patient suffering from a condition such as Rheumatoid arthritis. Bank *et al* teaches Melittin has anti-inflammatory mechanism and this may be why therapeutic properties have long been attributed to bee venom, especially in arthritic conditions (Seep age 403, first paragraph, in particular). The term "comprising" is open-ended. It expands the claimed composition to include additional protein. The '887 patent teaches that bee venom is useful for reducing pain associated with DNA virus infection (See claim 1 of '887 patent, summary of invention, column 4, lines 32-34, in particular). Kim et al teach that bee venom treatment significantly improves the relief of pain in osteoarthritis patients (See page 69, column 1, in particular) and an increase in joint mobility (See page 71, Discussion, in particular). The '901 patent teaches that any buffered anesthesia in sodium bicarbonate is useful for reducing pain associated with "bee sting like" injection due to local pH related tissue irritation (See column 15, lines 13-15, in particular). One having ordinary skill in the art would have been motivated to not to administer anesthetics topically because Koyama *et al* teach that topical application of anesthetics such as lidocaine is not effective for pain but markedly suppresses both the increase in the peak temperature and the area of temperature increase at the site of injection (See abstract, in particular). The '863 patent teaches the use of local anesthetic such as 2 to 4% lidocaine as local anesthetic to reduce the pain and discomfort caused by the bee stings thereby "calming" the victim (See column 2, lines 6-10, column 2, line 55, in particular). Cerrati *et al* teach the positive effects of bee venom on MS includes less fatigue and fewer muscle spasms (See page 57, column 2, in particular) and melittin slows down the body's inflammatory response inhibiting the amount of free radicals generated by tissues (See page 57, column 1, in particular). The recitation of administering bee venom and anesthetic simultaneously is an obvious variation of administering bee venom and anesthetic consecutively as taught by Steigerwaldt *et al.* The '901 patent teaches a method of reducing pain at the site of injection of by administering buffered anesthetics such as lidocaine, mepivacaine, bupivacaine and NEUTRA-CAINE (See entire document, abstract, in particular). Koyama *et al* teach pain can be measure using visual analog scale. Claims 43 and 44 are included in this rejection because the enzyme activity of Hyluronidase such as inhibiting gelatin induced aggregation of erythrocytes of about 3-5mm/H is the inherent properties of the enzyme itself and

the dilution of enzyme such that it exhibits about 40 to 100HHU/ml is within the purview of one skill in the art as taught by Steigerwaldt *et al.*

Applicants' arguments filed 10/15/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) there is no suggestion or motivation to combine and not by the use of hindsight in view of the present application. (2) Even assuming that Steigerwaldt can be combine with Cerrati, the combination does not teach or suggest the use of such a small amount of anesthetic to "reduce the pain of the patient by at least 57 on a visual analog scale" (3) Steigerwaldt does not teach or suggest the use of an anesthetic in an amount of 0.1 to 0.3 mg per injection.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the use of bee venom to treat pain is taught by the '887 patent (See entire document). Steigerwaldt et al teach the use of bee venom and anesthetic to treat pain that is associated with inflammatory condition such as Rheumatoid arthritis. The use of bee venom to treat pain associated with Rheumatoid arthritis and Multiple sclerosis is taught by Cerrati *et al.* The '901 patent the use of buffer anesthetic for reducing patient discomfort in patient in the form of "bee sting like" pain due to local pH related tissue irritation (See column 15, lines 13-15, in particular) and buffering anesthetic instantly before its use for reducing pain at the site of injection without sacrificing the normal two or more years of shelve life of these anesthetic (See column 2, lines 22-50, in particular).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to Applicants' argument that the combination does not teach or suggest the use of such a small amount of anesthetic to "reduce the pain of the patient by at least 57 on a visual analog scale", The '901 patent teaches a method of reducing pain at the site of injection of by administering buffered anesthetics such as lidocaine, mepivacaine, bupivacaine and NEUTRA-CAINE (See entire document, abstract, in particular). Koyama *et al* teach pain can be measure using visual analog scale. Kim *et al* teach a method of reducing pain by administering bee venom to a patient suffering from a condition such as pain associated with rheumatoid arthritis or osteoarthritis wherein the been venom is injected intradermally at 0.05 to 0.1 ml of standard BV-10 per injection to reduce pain of the patient by at least 57 on a visual analog scale where the degree of pain (VAS 50-60 is rated as moderate and 70-80 is rated as severe (See page 68, Methods, Fig 1, page 69, column 1, in particular). Further, the term "57 on a visual analog scale" is relative and is not clear it is relative to what and tolerance of pain also varies from one patient to the next.

In response to Applicants' argument that Steigerwaldt does not teach or suggest the use of an anesthetic in an amount of 0.1 to 0.3 mg per injection, the '901 patent teaches that standard local anesthetics come in the form of 0.25% to 0.75% in solution (See column 5, in particular) and serum lidocaine levels exceeded 2.5μg/ml within 5 minutes following intravenous injection is toxic as lidocaine cross the placenta and intradermal or subcutaneous injection is not likely to induce toxic blood level (See column 15, lines 1-12, in particular). Koyama *et al* teach that topical application of anesthetics such as lidocaine is not effective for pain but markedly suppresses both the increase in the peak temperature and the area of temperature increase at the site of injection (See abstract, in particular). From the combined teachings of the '901 patent, Koyama *et al* and Steigerwaldt et al, the recitation of the use of anesthetic in an amount of 0.1 to 0.3 mg per injection is within the purview of one ordinary skilled in the art at the time the invention was made as taught by the '901 patent, Koyama *et al* and Steigerwaldt *et al*.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

12. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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